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(57) Abstract

The present invention provides compounds having the structure: Ar_1–Q–Ar_2–O–$(CH_2)_n$–Z and pharmaceutically acceptable salts and stereoisomers thereof that are useful in the treatment of inflammatory diseases which are mediated by LTB_4 production, such as psoriasis, ulcerative colitis, IBD, and asthma.

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TITLE

LTA_4 HYDROLASE INHIBITORS

Field of the Invention

This invention relates generally to anti-inflammatory compounds and pharmaceutical compositions, and more particularly to anti-inflammatory compounds and compositions which are capable of inhibiting leukotriene A_4 hydrolase.

Background of the Invention

LTA_4 hydrolase is a requisite enzyme in the biosynthetic pathway leading to LTB_4 formation. LTB_4 is a proinflammatory compound. R. Lewis, et al., *N. Engl. J. Med.* 323, 645-655 (1990) have demonstrated that LTB_4 is a potent granulocyte agonist inducing chemotaxis, aggregation, degranulation, adherence and priming of inflammatory cells for induction by other agonists. Binding of LTB_4 to receptors is stereospecific with two distinct classes of binding sites. A. Lin, et al., *Prostaglandins* 28, 837-849 (1984). A high affinity site [$4\text{-}5\times10^{-10}$ M] mediates chemotaxis and chemokinesis while lower affinity sites [$0.6\text{-}5\times10^{-7}$ M] stimulate granular secretion and oxidative burst. The LTB_4

receptor is associated with a GTP-binding protein that regulates affinity and transduces signals. T. Schepers, et al., *J. Biol. Chem.* 267, 159-165 (1992). Elevated LTB_4 levels have been reported for many diseases. Most prominently, elevated LTB_4 levels have been correlated to the pathology of inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis and in psoriasis. P. Sharon, et al., *Gastroent.* 86, 453-460; K. Lauritsen, et al., *Gastroent.* 95, 11-17 (1989); S. Brain, et al., *Br. J. Pharm.*, 83, 313-317 (1984). Other properties of LTB_4 which may contribute to disease processes are: stimulation of mucus secretion; stimulation of cytokine production; and the ability to act synergistically with other inflammatory mediators such as prostaglandins and cysteinyl leukotrienes thereby amplifying the inflammatory process.

B. Samuelsson, et al., *J. Biol Chem.*, 264, 19469-19472 (1989) have shown that LTB_4 biosynthesis from arachidonic acid involves the action of 2 enzymes, 5-lipoxygenase [5-LO] and LTA_4 hydrolase. 5-LO transforms arachidonic acid to 5-HPETE and subsequent formation of LTA_4, which is an unstable allylic epoxide intermediate which is enzymatically hydrolyzed by LTA_4 hydrolase to form the dihydroxy acid LTB_4.

LTA_4 hydrolase is distinct from cytosolic and microsomal epoxide hydrolases based on strict substrate requirements, product formation [5(S),12(R) vs. 5(S),6(R)] for mouse liver cytosolic epoxide hydrolase, and lack of inhibition by inhibitors of cytosolic epoxide hydrolase. LTA_4 hydrolase appears to be ubiquitously distributed in mammalian tissues even in cell types that do not express 5-LO, suggesting the importance of transcellular metabolism of LTA_4. While peptidomimetic compounds such as bestatin and captopril have been shown to exhibit LTA_4 hydrolase inhibitory

activity, they are not able to satisfy the requirement of a small organic compound which is capable of cellular penetration. It would therefore be very advantageous to be able to provide low molecular weight inhibitors of LTB_4 biosynthesis which preferably exhibit oral activity in vivo at desirably low concentrations.

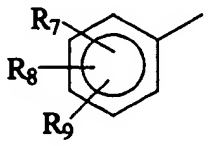
Summary of the Invention

Applicants have now discovered that compounds having the structure:

$$Ar_1\text{-}Q\text{-}Ar_2\text{-}O\text{-}(CH_2)_n\text{-}Z$$

and pharmaceutically acceptable salts and stereoisomers thereof possess LTA_4 hydrolase inhibitor activity, wherein

Ar^1 is an aryl moiety selected from the group consisting of:

(i) 

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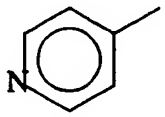
(ii) 

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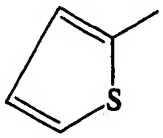
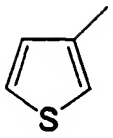
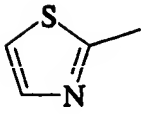
(iii) 

(iv)  , and

(v)  ;

Ar^2 is an aryl moiety selected from the group consisting of phenyl, mono-, di-, and tri-substituted phenyl, wherein the substituents are selected from the group consisting of Cl, Br, F, CF_3, lower alkyl, lower alkoxy, NH_2, NO_2, and OH;

Q is selected from the group consisting of:

(i) -O-;

(ii) $-CH_2-$,

(iii) $-OCH_2-$,

(iv) $-CH_2O-$,

(v) -NH-;

(vi) $-NHCH_2-$,

(vii) $-CH_2NH-$,

(viii) $-CF_2-$,

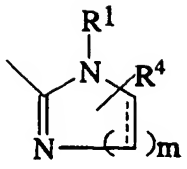
(ix) -CH=CH-,

(x) $-CH_2CH_2-$, and

(xi) carbon-carbon single bond;

n = 1, 2 or 3;

Z is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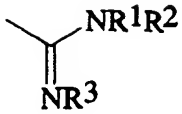
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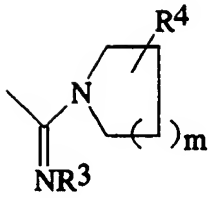
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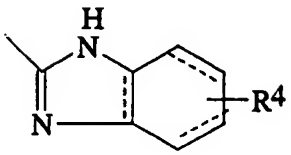
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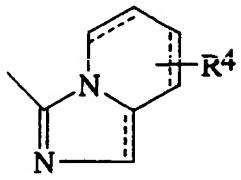


wherein

R^1, R^2 and R^3 are independently H, OH, lower alkyl, lower alkoxy, allyl, cyclic alkyl or $(CH_2)_p$-CO_2R^5 wherein p is an integer from 1 to 6;

R^4 is H, CO_2R^5, $CONH_2$, or COOH;

R^5 is H, lower alkyl, lower alkoxy, allyl or benzyl; -------- represents a single or double bond; and

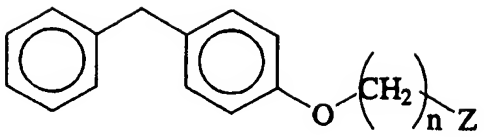
m is 1 or 2.

Detailed Description

In one of its embodiments, the present invention entails compounds having the structure:

$$Ar_1\text{-}Q\text{-}Ar_2\text{-}O\text{-}(CH_2)_n\text{-}Z$$

and pharmaceutically acceptable salts and stereoisomers thereof, wherein Ar_1, Q, Ar_2, Z, and n are as defined hereinbefore. In a preferred embodiment, the compounds of the present invention have the structure:



The compounds of the present invention, in several embodiments, may comprise a carboxylic acid or ester moiety. It will be appreciated by those of ordinary skill in the art

that a compound of the present invention comprising an ester moiety is readily converted, *in vivo*, especially when administered orally, into its corresponding carboxylic acid form. The ester-containing compounds of the present invention are therefore prodrugs of their carboxylic acid form.

In another of its aspects, the invention entails pharmaceutical composition comprising a pharmacologically effective amount of one or more of the compounds defined above and a pharmaceutically acceptable carrier.

In still another of its embodiments the present invention involves a method for treating a mammal exhibiting an LTB4 mediated inflammatory condition comprising administering to the mammal a pharmacologically effective amount of one or more of the compounds defined above.

The term "lower alkyl" means straight or branched chain alkyl having 1 to 6 carbon atoms such as methyl, ethyl, propyl, butyl, pentyl, hexyl and the branched chain isomers thereof. The term "lower alkoxy" means straight or branched chain alkoxy having 1 to 6 carbon

atoms such as methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and the branched chain isomers thereof. The term "cyclic alkyl" as used herein refers to non-aromatic alkyl ring structures, including multi-ring structures such as bicyclic and tricyclic rings, having between 5 and 20 carbon atoms. The term "allyl" as used herein means the 1-propenyl radical, $-CH_2-CH_2=CH_2$. The term "halo" or "halogen" means fluoro, chloro, bromo, or iodo.

Included within the classes and subclasses of compounds defined above are isomeric forms of the described compounds including diastereoisomers, enantiomers and tautomeric forms of the described compounds. Pharmaceutically acceptable salts of such compounds are also included as well as pharmaceutically acceptable salts of such isomers and tautomers.

In the structures disclosed herein, a bond drawn across a bond in a ring indicates that the bond can be to any available atom of the ring structure.

The expression "pharmaceutically acceptable salts" is intended to include those salts capable of being formed with the compounds of the present invention without materially altering the chemical structure or pharmacological properties thereof. Such salts can be inorganic and organic cations or acid addition salts, and included, but are not limited to, sodium, potassium, calcium, ammonium, alkylammonium, quaternary ammonium, triethanolamine, lysine, hydrochloride, hydrobromide, and others well known to those of ordinary skill in the art. The foregoing salts are prepared in the conventional manner by neutralization of the compounds defined above with the desired base or acid.

The compounds of the present invention can be administered to a subject in such oral dosage forms as tablets, capsules, pills, powders, granules, elixirs or syrups, as well as aerosols for inhalation. Likewise, administration may be effected intravascularly, subcutaneously, or intramuscularly using dosage forms known to those of ordinary skill in the pharmaceutical arts. In general, the preferred form of administration is oral. An effective but non-toxic amount of the compound is employed in treatment. The dosage regimen utilizing the present compounds is selected in accordance with a variety of factors including the type, age, weight, sex and medical condition of the patient; the severity of the condition to be ameliorated; and the route of administration. A physician of ordinary skill can readily determine and prescribe a "pharmaceutically effective amount" of one or more of the compounds defined above, that is, the effective amount of a compound required to prevent, treat or arrest the progress of the condition. Dosages of the compounds of the present invention will range generally between 0.1 mg/kg/day to about 100 mg/kg/day and preferably between about 0.5 mg/kg/day to about 50 mg/kg/day when administered to a subject suffering from allergic or hypersensitivity reactions or inflammation. The compounds may also be administered transdermally or topically to treat proliferative skin conditions such as psoriasis. The daily dosage may be administered in a single dose or in equal divided doses, for example, three to four times daily. The "subject" is typically a mammal and, in particular, a human patient.

As used herein the phrase "LTA_4 hydrolase inhibitor" means a compound that is capable of exhibiting an IC_{50} of less than 1 mM in an in vitro assay employing 10 μg/ml of LTA_4 hydrolase enzyme (specific activity 600

nMoles LTB_4/min/mg of enzyme) in the presence of 25 μM substrate (LTA_4) in a total reaction volume of 100 μl.

In the pharmaceutical compositions and methods of the present invention, at least one of the active compounds defined above or a pharmaceutically acceptable salt thereof will typically be administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier materials") suitably selected with respect to the intended form of administration and consistent with conventional pharmaceutical practices. For example, the pharmaceutical compositions of this invention can be administered as oral tablets, capsules, elixirs, syrups and the like. For oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol and the like; for oral administration in liquid form, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as ethanol and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintigrating agents and coloring agents can also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Lubricants for use in these dosage forms include boric acid, sodium benzoate, sodium acetate, sodium chloride and the like. Disintigrators include, without limitation, starch, methylcellulose, agar, bentonite, guar gum and the like.

By virtue of their activity as LTA_4 hydrolase inhibitors, the compounds defined above are useful in treating inflammatory conditions mediated by LTB_4 production in mammals such as psoriasis, contact and atropic dermatitis, Crohn's disease, ulcerative colitis, inflammatory bowel disease, multiple sclerosis, ankylosing spondylitis, arthritis, asthma and the like. Similarly, the compounds defined above can be used in preventing recurring inflammatory attacks. A physician or veterinarian of ordinary skill can readily determine whether a subject exhibits the inflammatory condition. A preferred utility relates to treatment of ulcerative colitis.

Among the compounds of the present invention are the following:

α-[[4-(phenylmethyl)phenoxy]methyl]-1-piperidinemethanimine, monohydrochloride;

α-[[4-(phenylmethyl)phenoxy]methyl]-1-pyrrolidinemethanimine, monohydrochloride;

ethyl 1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperdinecarboxylate, monohydrochloride;

ethyl 3-[[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]amino]propanoate, monohydrochloride;

4,5-dihydro-2-[[4-(phenylmethyl)phenoxy]methyl]-1H-imidazole;

1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl-4-piperidinecarboxyamide;

1-imino-2-[4-(phenylmethyl)phenoxy]ethanamine;

α-[3-[4-(phenylmethyl)phenoxy]propyl]-1-piperidinemethanimine, monohydrochloride;

4,5-dihydro-2-[3-[4-(phenylmethyl)phenoxy]propyl]-1H-imidazole;

3a,4,5,6,7,7a-hexahydro-2-[[4-(phenylmethyl)phenoxy]propyl]-1H-benzimidazole;

2-[4-(phenylmethyl)phenoxy]-N-(tricyclo[3.3.1.1 3,7]decan-2-yl)ethanimidine, monohydrate;

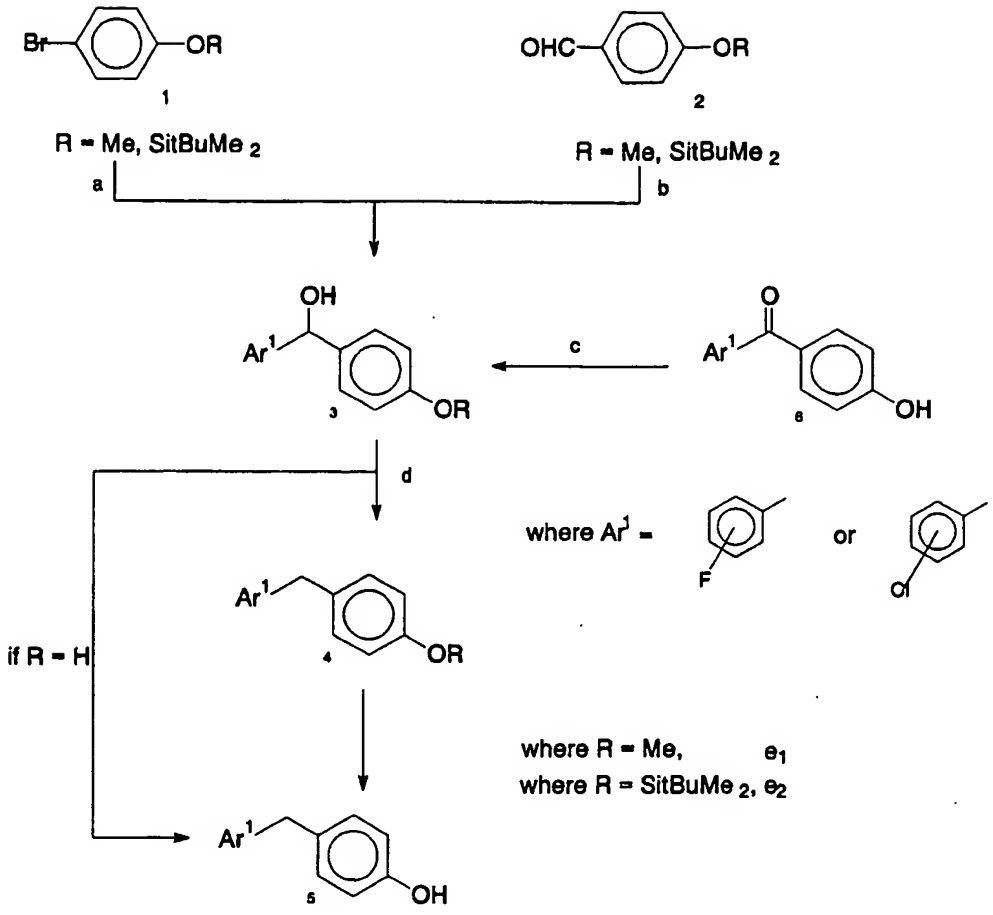
N'-hydroxy-2-[4-(phenylmethyl)phenoxy]ethanimidamide.

The compounds of the invention are prepared from readily available starting materials by any of the following alternate processes in a conventional manner. The following reaction schemes describe methods which can be employed for preparing the compounds defined above, including starting materials, intermediates and reaction conditions. The following terms, as used herein, have the following definitions:

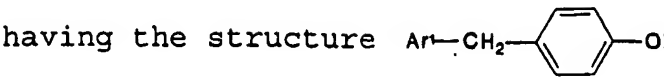
NMMO	N-methylmorpholine-N-oxide
Me	methyl
$SitBuMe_2$	t-butyldimethylsilyl
nBuLi	n-butyllithium
THF	tetrahydrofuran
Et_2O	diethyl ether
EtOH	ethyl alcohol
Pd/C	palladium on carbon
TFA	trifluoroacetic acid
Et_3SiH	triethylsilane
TBAF	tetrabutylammonium fluoride
DMF	dimethylformamide
nBu_4NBr	tetra-n-butylammonium bromide
TsCl	tosylchloride or p-toluenesulfonyl-chloride
TsO	tosylate or p-toluenesulfonate
MeOH	methyl alcohol
AcOH	acetic acid
Bn	benzyl
DEAD	diethylazodicarboxylate
Ph_3P	triphenylphosphine
MCPBA	metachloroperbenzoic acid
LAH	lithium aluminum hydride
TsOH	tosic acid or p-toluenesulfonic acid
LDA	lithium diisopropylamide

DSC	disuccinylcarbonate
nBuOH	n-butyl alcohol
TFAA	trifluoroacetic anhydride
Me_3SnN_3	trimethyl-tin azide
TMS	trimethyl silyl
Ac_2O	acetic anhydride
Ac	acetate
EtOAc	ethyl acetate
Hep	heptane

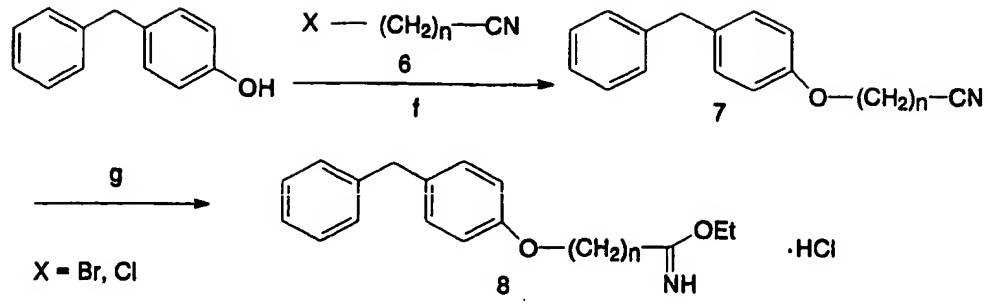
Scheme 1

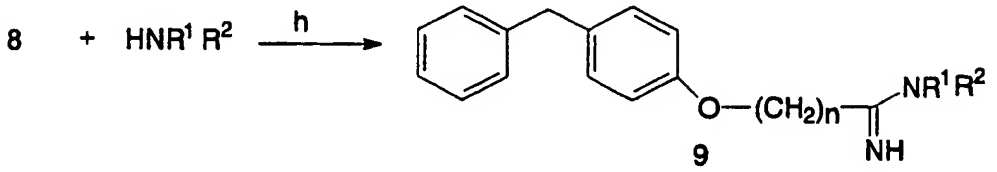


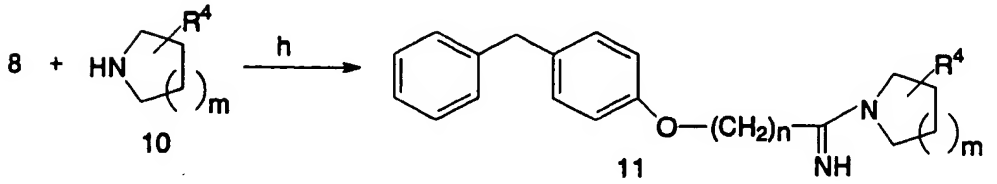
a) nBuLi, THF, -78°C; Ar^1CHO.
b) Ar^1Li or Ar^1MgBr, Et_2O, -78°C.
c) EtOH, $NaBH_4$.
d) EtOH, 4% Pd/C, H_2 or CH_2Cl_2, TFA, Et_3SiH.
e^1) BBr_3, CH_2Cl_2, -78°C.
e^2) THF, TBAF.

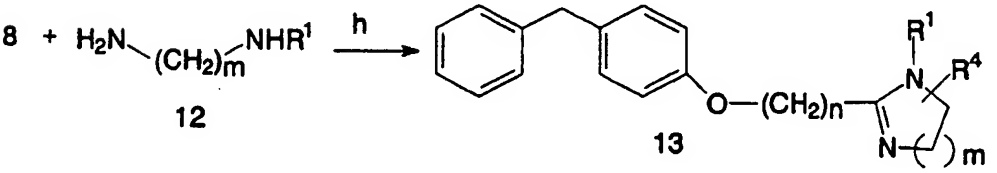
Scheme 1 shows methods for producing compounds having the structure  . Scheme 1 shows two related precursor compounds (**1**, **2**) which may be employed as a starting material. Compound **1** is an alkylated or silylated derivative of p-bromophenol. A convenient starting material **1** is 1-bromo,4-methoxybenzene (i.e., R is methyl). On the other hand, compound **1** may be readily provided by silylation of p-bromophenol with t-butyldiphenylsilyl chloride or other silylating agents. In either event, compound **1** may be reacted with tert-butyl lithium in an ethereal solvent at low temperature, such as in THF at -78°C, and quenched with an arylaldehyde (Ar^1CHO) to yield compound **3**. Similarly, starting from compound **2**, a p-methoxybenzaldehyde or a silylated derivative of p-hydroxybenzaldehyde may be employed. Compound **2** may be reacted with an aryl lithium (Ar^1Li) or aryl magnesium bromide (Ar^1MgBr) to yield compound **3**. Regardless of which route is chosen, compound **3** is reduced, e.g., by hydrogenation over palladium on carbon or with triethylsilane, to provide compound **4**. Compound **4** is readily deprotected using TBAF in THF (desilylation) or using BBr_3 in methylene chloride at -78°C (dealkylation) to provide compound **5**, 4-hydroxydiphenylmethane.

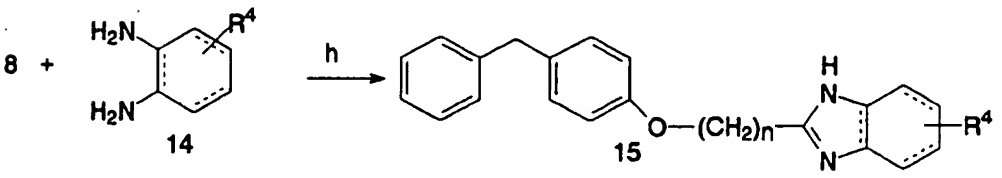
Scheme 2

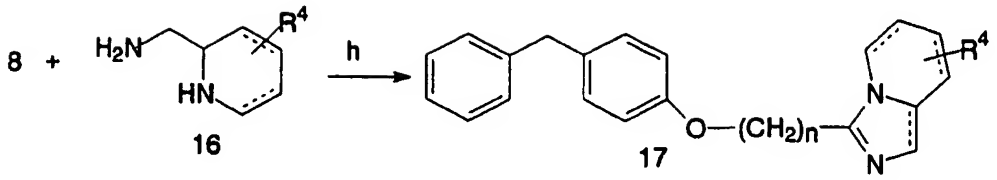

X — (CH2)n—CN
6
f
OH
7
O—(CH2)n—CN
g
X = Br, Cl
OEt
O—(CH2)n
NH
8
·HCl

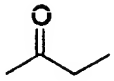

8 + HNR1 R2
h
NR1 R2
O—(CH2)n
NH
9


8 +
HN
R4
m
10
h
O—(CH2)n
N
R4
m
NH
11


8 + H2N
(CH2)m
NHR1
12
h
R1
N
R4
O—(CH2)n
N
m
13


8 +
H2N
H2N
R4
14
h
H
N
O—(CH2)n
N
R4
15

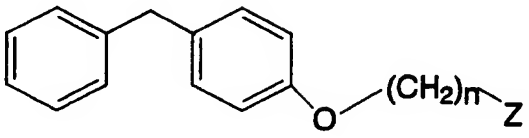


f)  , 80°C, K_2CO_3

g) HCl/EtOH, 0°C

h) EtOH

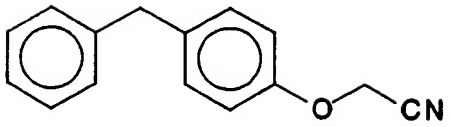
Scheme 2 shows methods for preparing compounds having the general formula:



wherein Z and n are as defined hereinbefore.

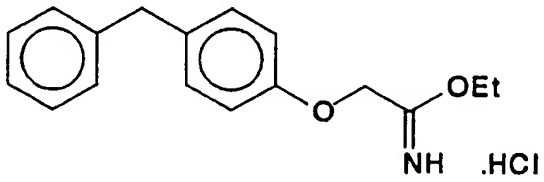
4-hydroxydiphenylmethane may be reacted with an alkylnitrile halide of compound 6 in the presence of a base, for example, K_2CO_3, in a solvent, for example, methyl ethyl ketone, and reflux at 80°C for 18 hours to yield compound 7. Addition of dry hydrogen chloride to compound 7 in ethanol may provide imidates, compound 8. Compound 8 may be reacted with ammonia or primary or secondary amines, in ethanol, to afford amidines, compound 9. Compound 8 may be also reacted with compounds 10, 12, 14 and 16 to generate corresponding compounds 11, 13, 15 and 17, wherein R^1, R^2, R^4, n and m are as defined hereinbefore.

Example 1



To a stirred solution of 4-hydroxydiphenylmethane (20 g, 0.11 mol) in methyl ethyl ketone (100 mL) was added chloroacetonitrile (8.3 g, 0.11 mol) and potassium carbonate (50 g, 0.36 mol) and the mixture was refluxed at 80°C for 18 hours. The solvent was removed under reduced pressure. The residue was taken up in water, extracted twice with ether and the combined organic layers were washed 4 times with 5% NaOH, water and brine, and then dried (Na_2SO_4) and concentrated in vacuo to give the title compound as brown oil (23.5 g). The resulting product was fully characterized in the next step (Example 2).

Example 2



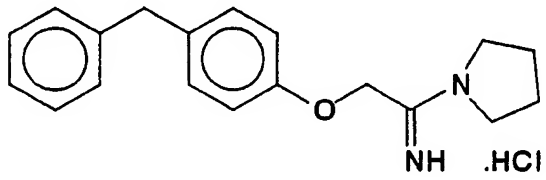
To a stirred solution of the compound of Example 1 (23.5 g, 0.1 mol) in chloroform (60 mL) was added absolute ethanol (5 g, 0.11 mol) and the solution was cooled in the reaction flask on an ice bath. A stream of hydrogen chloride gas was introduced into the reaction mixture until the required amount of HCl (4 g, 0.11 mol) was absorbed. The flask was tightly sealed and stored in the refrigerator overnight. A white solid was filtered and washed several times with ether and then recrystalized from ethanol/ether to afford the

title compound as white crystals (15 g). The product had the following properties:

Analysis calculated for $C_{17}H_{20}NO_2Cl + 0.3H_2O$: Calc: C, 65.61; H, 6.67; N, 4.50. Found: C, 65.63; H, 6.41; N, 4.47.

Example 3

α-[[4-(phenylmethyl)phenoxy)methyl]-1-pyrrolidinemethanimine, monohydrochloride

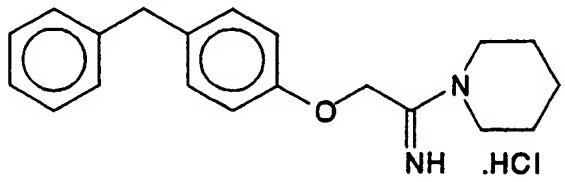


To a solution of the compound of Example 2 (1 g, 3.3 mmol) in ethanol (5 mL) was added pyrrolidine (306 mg, 4.3 mmol) and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the solid was recrystallized from ethanol/ether to give the title compound as white crystals (520 mg). The product had the following properties:

Analysis calculated for $C_{19}H_{23}N_2OCl + 0.3H_2O$: Calc: C, 67.87; H, 7.07; N, 8.33. Found: C, 67.91; H, 6.93; N, 8.27.

Example 4

α-[[4-(phenylmethyl)phenoxy)methyl]-1-peperidinemethanimine, monohydrochloride

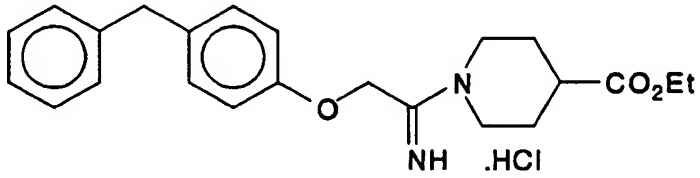


This compound was prepared by the method given in Example 3 using piperdine in place of pyrrolidine to afford the title compound as white crystals. The product had the following properties:

Analysis calculated for $C_{20}H_{25}N_2OCl$: Calc: C,69.65; H, 7.31; N, 8.12. Found: C,69.29; H, 7.12; N, 7.93.

Example 5

ethyl 1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidinecarboxylate, monohydrochloride

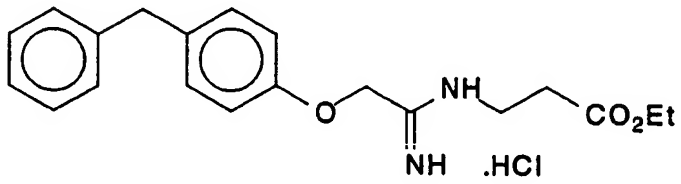


This compound was prepared by the method given in Example 3 using ethyl isonipecotate in place of pyrrolidine to afford the title compound as white crystals. The product had the following properties:

Analysis calculated for $C_{23}H_{29}N_2O_3Cl$: Calc: C, 66.26; H, 7.01; N, 6.72. Found: C, 65.86; H, 6.98; N, 6.63.

Example 6

ethyl 3-[[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]amino]propanoate, monohydrochloride

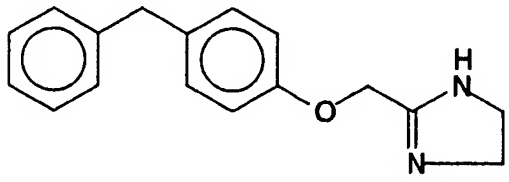


To a solution of the compound of Example 2 (0.5 g, 1.6 mmol) in ethanol (5 mL) was added beta-alanine ethyl ester hydrochloride (307 mg, 2.0 mmol) and triethylamine (202 mg, 2 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue was dissolved in ethanol and ether was added until a white solid formed. The mixture was filtered and the filtrate was concentrated and purified by preparatory silica gel plates eluting with $CHCl_3/EtOH/NH_4OH$ (84/15/1) to give the title compound as white crystals (30 mg). The product had the following properties:

Analysis calculated for $C_{20}H_{25}N_2O_3Cl$ + 0.9 H_20: Calc: C, 61.11; H, 6.87; N, 7.13. Found: C, 61.04; H, 6.38; N, 7.27.

Example 7

4,5-dihydro-2-[[4-(phenylmethyl)phenoxy]methyl]-1H-imidazole

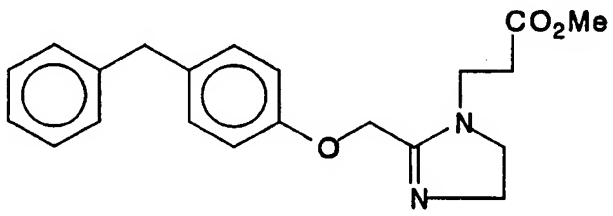


To a stirred solution of the compound of Example 2 (0.5 g, 1.6 mmol) in ethanol (5 mL) was added ethylenediamine (1 mL). The mixture was refluxed under

argon for 8 hours and then cooled to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in methanol. Ether was added until a white percipitate formed which was filtered, and the filtrate was concentrated and then purified by preparatory silica gel plates eluting with $CHCl_3/EtOH/NH_4OH$ (84/15/1) to give the title compound as a white solid (180 mg). The product had the following properties:

Analysis calculated for $C_{17}H_{18}N_2O$ + 0.5 H_2O: Calc: C, 74.16; H, 6.95; N, 10.17. Found: C, 74.01; H, 6.69; N, 10.10.

Example 8

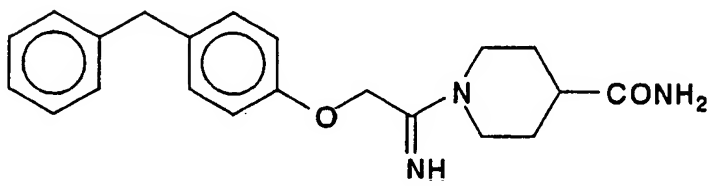


To a solution of the compound of Example 7 (70 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) was added methyl acrylate (27 mg, 0.31 mmol). The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by preparatory silica gel plates eluting with $CHCl_3/EtOH/NH_4OH$ (90/10/0.5) to afford the title compound as yellow oil (15 mg). The product had the following properties:

Analysis calculated for $C_{21}H_{24}N_2O_3$ + 1.1 H_2O: Calc: C, 67.76; H, 7.09; N, 7.53. Found: C, 67.75; H, 6.96; N, 7.50.

Example 9

1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidinecarboxamide

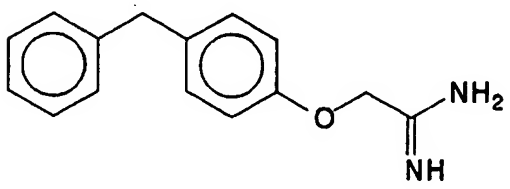


To a stirred solution of the compound of Example 2 (305 mg , 1 mmol) in ethanol (3 mL) and methanol (3 mL) was added isonipecotamide (128 mg, 1 mmol). The mixture was refluxed under argon overnight. Then the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in 1N NaOH and extracted three times with CH_2Cl_2. The combined organic layers were washed with water, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The solid was recrystallized from methanol/ether to give the title compound as white crystals (80 mg). The product had the following properties:

Analysis calculated for $C_{21}H_{25}N_3O_2$ + 0.3 H_2O: Calc: C, 70.68; N, 7.23; N, 11.78. Found: C, 70.82; H, 6.60; N, 11.82.

Example 10

1-imino-2-[4-(phenylmethyl)phenoxy]ethanamine



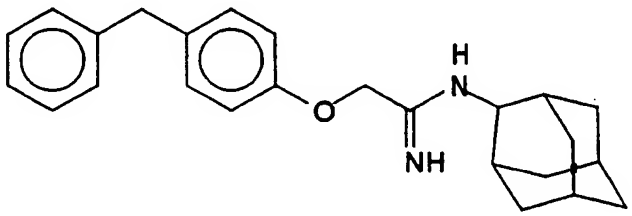
To a solution of the compound of Example 2 (305 mg, 1 mmol) in ethanol (3 mL) was added a solution of 9% NH_3 in ethanol (0.3 mL), and the mixture was stirred at

room temperature overnight. The mixture containing a white precipitate was filtered and the filtrate was concentrated. The residue was dissolved in 1N NaOH and extracted three times with CH_2Cl_2. The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The white solid obtained was triturated with ether to give pure title compound which had the following properties:

Analysis calculated for $C_{15}H_{16}N_2O$ + 0.1 H_2O: Calc: C, 74.42; H, 6.74; N, 11.57. Found: C, 74.51; H, 6.67; N, 11.49.

Example 11

2-[4-(phenylmethyl)phenoxy]-N-(tricyclo[3.3.1.1 3,7]decan-2-yl)ethanimidamide, monohydrate

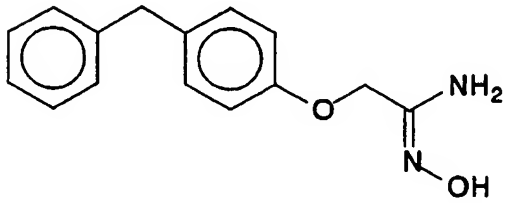


To a solution of the compound of Example 2 (458 mg, 1.5 mmol) in ethanol (10 mL) was added 2-adamantanamine hydrochloride (281 mg, 1.5 mmol) and triethylamine (152 mg, 1.5 mmol), and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with $CHCl_3$/EtOH/NH_4OH (92/7/0.5) to give the title compound as yellow solid (320 mg). The product had the following properties:

Analysis calculated for $C_{25}H_{30}N_2O$ + 1 H_2O: Calc: C, 76.50; H, 8.22; N, 7.14. Found: C, 76.43; H, 7.90; N, 7.11.

Example 12

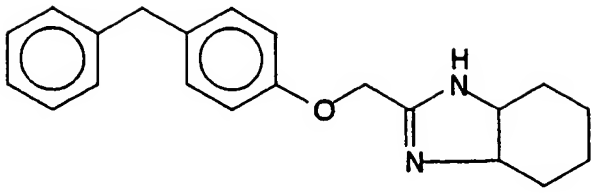
N'-hydroxy-2-[4-(phenylmethyl)phenoxy]ethanimidamine



To a stirred solution of the compound of Example 1 (1g, 4.5 mmol) in ethanol (20 mL) was added hydroxylamine hydrochloride (312 mg, 4.5 mmol) and triethylamine (454 mg, 4.5 mmol) and the mixture was refluxed for 4 hours. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in water and extracted three times with ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with hexane/ethyl acetate (4/1) to give the title compound as yellow crystals. (0.5 g). The product had the following properties:

Analysis calculated for $C_{15}H_{16}N_2O_2$: Calc: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.51; H, 6.30; N, 10.81.

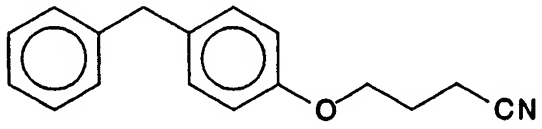
Example 13



To a stirred solution of the compound of Example 2 (0.5 g, 1.6 mmol) in ethanol (5 mL) was added 1,2-diaminocyclohexane (182 mg, 1.6 mmol) and the mixture was refluxed for 5 hours. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by preparatory silica gel plates eluting with $CHCl_3/EtOH/NH_4OH$ (90/10/1) to give the title compound as yellow oil (100 mg). The product had the following properties:

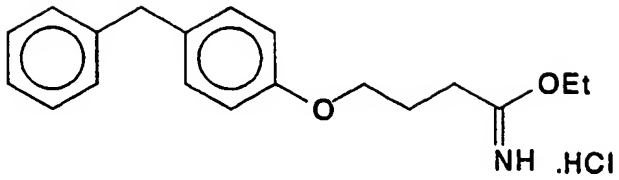
Analysis calculated for $C_{21}H_{24}N_2O$ + 0.9 H_20: Calc: C, 74.92; H, 7.72; N, 8.32. Found: C, 74.82; H, 7.77; N, 8.24.

Example 14



The method decribed in Example 1 was employed, except that 4-bromobutyronitrile was used in place of chloroacetonitrile, to afford the title compound as a yellow oil. The resulting product was fully characterized in the next step (Example 15).

Example 15

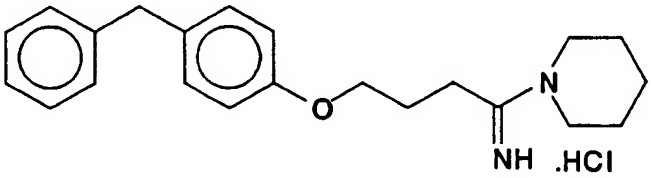


The method described in Example 2 was carried out using the compound of Example 14 in place of the compound of Example 1 to afford the title compound as white crystals. The product had the following properties:

Analysis calculated for $C_{19}H_{24}NO_2Cl$: Calc: C, 68.36; H, 7.25; N, 4.20. Found: C, 68.43; H, 6.90; N, 4.10.

Example 16

α-[3-[4-(phenylmethyl)phenoxy)propyl]-1-peperidinemethanimine, monohydrochloride

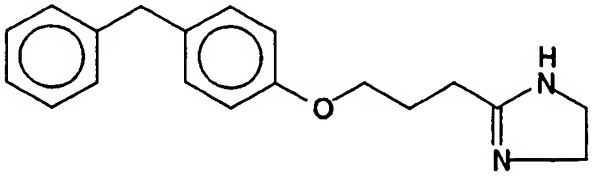


The method described in Example 3 was carried out using the compound of Example 15 in place the compound of Example 2 to afford the title compound as white crystals. The product had the following properties:

Analysis calculated for $C_{22}H_{29}N_2OCl$: Calc: C, 70.85; H, 7.84; N, 7.51. Found: C, 70.59; H, 7.90; N, 7.61.

Example 17

4,5-dihydro-2-[[4-(phenylmethyl)phenoxy] methyl]-1H-imidazole



To a stirred solution of the compound of Example 15 (0.5 g, 1.5 mmol) in ethanol (5 mL) was added ethylenediamine (1 mL) and the mixture was refluxed under argon for 8 hours. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in 5% K_2CO_3 and extracted three times with CH_2Cl_2. The combined organic layers were washed with water and brine, dried with Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by preparatory silica gel plates eluting with 2% NH_4OH/MeOH to give the title compound as yellow solid (50 mg). The product had the following properties:

Analysis calculated for $C_{19}H_{22}N_2O$ + 0.4 H_2O: Calc: C, 75.67; H, 7.62; N, 9.29. Found: C, 75.68; H, 7.58; N, 9.20.

LTA Hydrolase Methods

The following Table presents data demonstrating the pharmacological activity of the LTA hydrolase inhibitors of the present invention. One or more of three different assays, (1) an in vitro LTA hydrolase enzyme assay, (2) a human whole blood assay utilizing calcium ionophore stimulation, and (3) a murine ex vivo assay utilizing calcium ionophore stimulation were employed to determine the level of LTA hydrolase inhibitor activity.

Recombinant Human LTA Hydrolase Assay for LTA Hydrolase Inhibitor Activity

Compounds of the present invention were tested for LTA hydrolase inhibitor activity against recombinant human LTA hydrolase (rhLTAH). Recombinant human LTA hydrolase-encoding vectors were prepared and used to express rhLTAH essentially as described by J. Gierse, et al., *Protein Expression and Purification*, 4, 358-366 (1993). Briefly, LTA hydrolase encoding DNA was amplified by polymerase chain reaction using a pair of oligonucleotide primers based on the nucleotide sequence from the 5'-end, and the complement of the 3'-end, of the coding region of the LTA hydrolase gene, the nucleotide sequence of which gene is known. (See, C. Funk, et al., Proc. Natl. Acad. Sci. USA 84, 6677-6681 (1987)). A λgt11 human placental cDNA library (Clonetech, Palo Alto, CA) provided the nucleic acid template. The LTA hydrolase encoding region had a length of about 1.9 kb. The amplified 1.9 kb DNA was isolated and cloned into the genomic baculovirus, *Autographa californica* nuclear polyderosis virus (AcNPC) DNA, and the baculovirus expression vector was transfected into Spodoptera frugiperda Sf-9 cells employing the calcium phosphate co-precipitation method (see, M. Summers, et al., Tex. Agric. Exp. Stn. Bull. 1555, 1-57 (1987). Recombinant LTA_4 hydrolase enzyme was purified from the transfected Sf-9 cells essentially as described by J. Gierse, et al., supra.

One or more predetermined amounts of a compound of the invention were incubated in assay buffer (0.1 M potassium phosphate, 5 mg/ml fatty acid free BSA, 10% DMSO, pH 7.4) for 10 minutes at room temperature with 250 ng of recombinant $hLTA_4H$ to allow binding, if any, between the enzyme and inhibitor. The stock enzyme solution was 1 mg/m. LTA_4 hydrolase, 50 mM Tris, pH

8.0, 150 mM NaCl, 2.5 mM beta-mercaptoethanol, 50% glycerol. The specific activity of the enzyme was about 650 nMoles/min/mg. LTA_4 (i.e., substrate) was prepared from the methyl ester of LTA_4 (Biomol, Inc., Plymouth Meeting, PA) by treating the methyl ester with 30 molar equivalents of LiOH at room temperature for 18 hours. The LTA_4 substrate in its free acid form was kept frozen at -80°C until needed. LTA_4 (free acid) was thawed and diluted in assay buffer (minus DMSO) to a concentration of 350 ng/ml and 25 μl (8ng) of LTA_4 substrate was added to the reaction mixture (total volume of reaction mixture = 200 μl at time zero. Each reaction was carried out at room temperature for 10 minutes. The reaction was stopped by diluting 25 μl of the reaction mixture with 500 μl of the assay buffer without DMSO. LTA_4 was quantified in the diluted sample by a commercially available enzyme-linked immunoassay [Caymen Chemical Col. Ann Arbor, MI] using the method recommended in the manufacturer's instructions and compared to the amount of LTA_4 produced in a negative control (i.e., essentially identical conditions except without addition of an inhibitor compound). The IC_{50} was routinely calculated from the data produced.

LTB_4 and Thromboxane Production by Calcium Ionophore Stimulated Human Blood for LTB_4 Hydrolase Inhibitor Activity

Human blood, collected in heparin-containing Vacutainer tubes, was diluted 1:4 with RPMI-1640 media and 200 μl of the diluted blood was added into each of a 96-well microtiter plate. One or more concentrations of the leukotriene A_4 hydrolase inhibitor compounds being tested were prepared (diluted in DMSO) and 2 μl added and gently mixed with the diluted whole blood. After incubating for 15 minutes at 37°C in a humidified incubator, calcium ionophore A13187 (Sigma Chemical

Co., St. Louis, MO) was added to a final concentration of 20 mcg/ml and the incubation continued under the same conditions for an additional 10 minutes to allow LTB_4 formation. The reaction was terminated by centrifugation (833 g, 10 minutes at 4°C) and supernatant were analyzed for LTB_4 and thromboxane by commercially available enzyme-linked immunoassays (Caymen Chemical Co., Ann Arbor, MI) according to the manufacturer's instructions. The IC_{50} of each test compound was determined from the amount of inhibition of LTB_4 production as compared to an essentially identical assay in which no inhibitor compound was present.

Ex Vivo LTB_4 and Thromboxane Production by Calcium Ionophore Stimulated Mouse Blood for LTB_4 Hydrolase Inhibitor Activity

Leukotriene A_4 hydrolase inhibitor compounds of the present invention were diluted to a predetermined concentration in phosphate buffered saline containing 2% DMSO and 1% Tween 80. The compounds were administered by oral gavage to adult male outbred mice weighing approximately 20-30 gm at a dose of 10 mg/kg body weight. (Compounds given at a dose of 50 mg/kg body weight are designated in following Table by the symbol, *) Sixty (60) minutes after administration of an LTA_4 inhibitor compound of the invention, blood was collected (into heparin-containing tubes) from the retroorbital sinus. The heparinized blood was added to the wells of a microtiter plate along with an equal volume of RPMI-1640 media, and calcium ionophore A23187 was added to a final concentration of 20 mcg/ml. The mixture was incubated for 10 minutes at 37°C in a humidified incubator. The reaction was terminated by centrifugation (833 g. 10 minutes at 4°C). Supernatant were analyzed for LTB_4 and thromboxane by commercially

available enzyme-linked immunoassays [Caymen Chemical Co., Ann Arbor, MI] in accordance with the manufacturer's instructions. The percent inhibition was determined by comparison to animals treated identically except that the solution administered by oral gavage was devoid of inhibitor compound.

LTA$_4$ HYDROLASE INHIBITOR ACTIVITY

Ex.#	Recombinant Human LTA$_4$ Hydrolase Assay IC_{50} LTA$_4$ (μM)	Inhibition of Calcium Ionophore-induced LTB$_4$ Production in Human Blood IC_{50} HWB (μM)	Murine Ex Vivo LTB$_4$ Inhibition %I LTB$_4$/at 1 hour after administration of 10mg/kg
3	0.004	0.053	46
4	0.0043	0.085	30
5	0.0013	0.071	62
6	0.023	0.2	54
7	0.07	0.22	33
8	1.17	0.55	68
9	0.017	0.077	30
10	0.089	0.19	0
11	7.8	-	-
12	>100	17.9	63
13	0.2	0.19	71
16	0.053	0.64	60
17	0.064	0.64	28

"-" means Not Determined

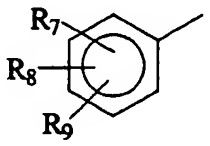
What is claimed is:

1. A compound having the structure:

$$Ar_1\text{-}Q\text{-}Ar_2\text{-}O\text{-}(CH_2)_n\text{-}Z$$

and pharmaceutically acceptable salts and stereoisomers thereof possess LTA_4 hydrolase inhibitor activity, wherein

Ar^1 is an aryl moiety selected from the group consisting of:

(i) 

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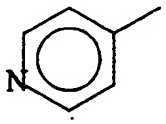
(ii) 

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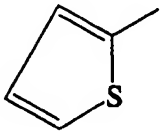
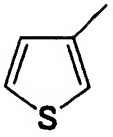
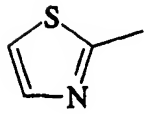
(iii) 

(iv) 

, and

(v) 

;

Ar^2 is an aryl moiety selected from the group consisting of phenyl, mono-, di-, and tri-substituted phenyl, wherein the substituents are

selected from the group consisting of Cl, Br, F, CF_3, lower alkyl, lower alkoxy, NH_2, NO_2, and OH;

Q is selected from the group consisting of:

(i) -O-;

(ii) $-CH_2-$,

(iii) $-OCH_2-$,

(iv) $-CH_2O-$,

(v) -NH-;

(vi) $-NHCH_2-$,

(vii) $-CH_2NH-$,

(viii) $-CF_2-$,

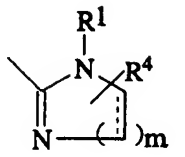
(ix) -CH=CH-,

(x) $-CH_2CH_2-$, and

(xi) carbon-carbon single bond;

n is 1, 2, or 3; and

Z is



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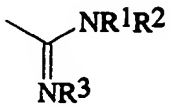

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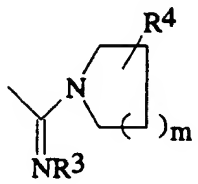
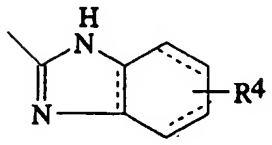


,



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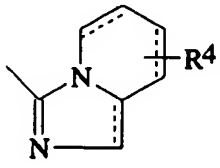


wherein

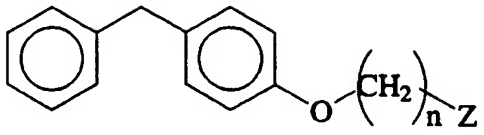
R^1, R^2 and R^3 are independently H, OH, lower alkyl, lower alkoxy, allyl, cyclic alkyl or $(CH_2)_p-CO_2R^5$ wherein p is an integer from 1 to 6;

R^4 is H, CO_2R^5, $CONH_2$, or COOH;

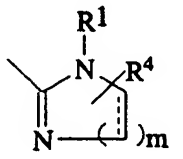
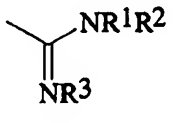
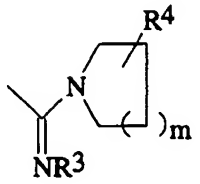
R^5 is H, lower alkyl, lower alkoxy, allyl or benzyl;

<u>--------</u> represents a single or double bond; and m is 1 or 2.

2. The compound of claim 1 having the structure:



and pharmaceutically acceptable salts and stereoisomers thereof, wherein n is 1, 2, or 3 and Z is


,

,

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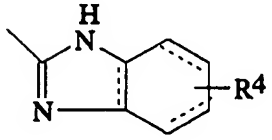
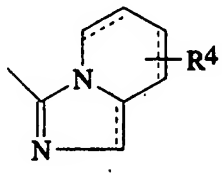

,


wherein

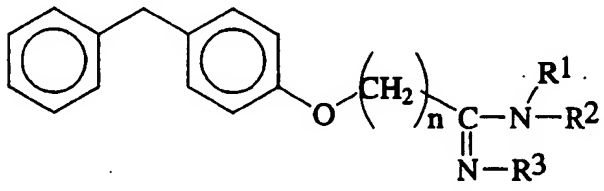
R^1, R^2 and R^3 are independently H, OH, lower alkyl, lower alkoxy, allyl, cyclic alkyl or $(CH_2)_p$-CO_2R^5 wherein p is an integer from 1 to 6;

R^4 is H, CO_2R^5, $CONH_2$, or COOH;

R^5 is H, lower alkyl, lower alkoxy, allyl or benzyl;

-------- represents a single or double bond; and m is 1 or 2.

3. The compound of claim 2 having the structure



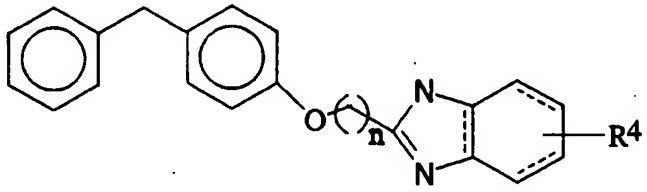
4. The compound of claim 2 wherein R^2 is $(CH_2)_mCO_2R^5$.

5. The compound of claim 4 wherein n is 1 and m is 2.

6. The compound of claim 2 wherein R^1 and R^2 are independently hydrogen, lower alkyl, or cyclic alkyl.

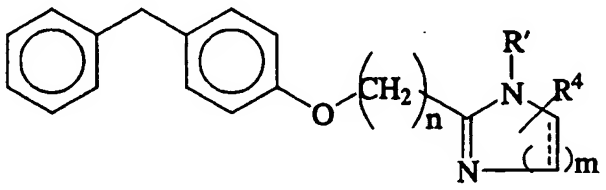
7. The compound of claim 5 wherein R^3 is hydrogen or hydroxyl.

8. The compound of claim 2 which has the structure:



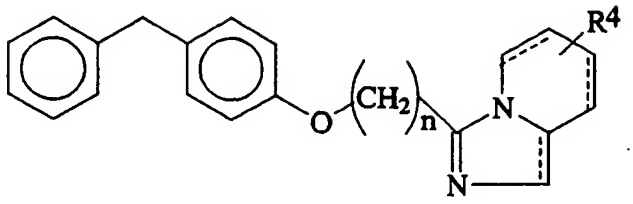
9. The compound of claim 8 wherein R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

10. The compound of claim 2 which has the structure:



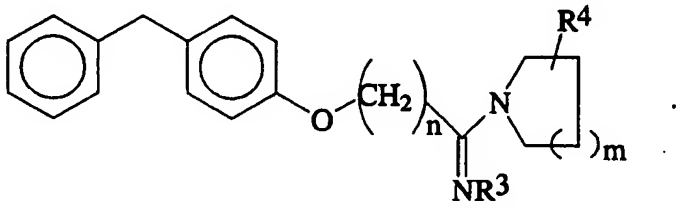
11. The compound of claim 10 wherein R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

12. The compound of claim 2 which has the structure:



13. The compound of claim 12 wherein R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

14. The compound of claim 2 which has the structure:



15. The compound of claim 14 wherein R^3 is hydrogen or hydroxyl and R^4 is H, $CONH_2$, or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

16. The compound of claim 2 chosen from the group consisting of:

α-[[4-(phenylmethyl)phenoxy]methyl]-1-piperidinemethanimine, monohydrochloride;

α-[[4-(phenylmethyl)phenoxy]methyl]-1-pyrrolidinemethanimine, monohydrochloride;

ethyl 1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperdinecarboxylate, monohydrochloride;

ethyl 3-[[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]amino]propanoate, monohydrochloride;

4,5-dihydro-2-[[4-(phenylmethyl)phenoxy]methyl]-1H-imidazole;

1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl-4-piperidinecarboxyamide;

1-imino-2-[4-(phenylmethyl)phenoxy]ethanamine;

α-[3-[4-(phenylmethyl)phenoxy]propyl]-1-piperidinemethanimine, monohydrochloride;

4,5-dihydro-2-[3-[4-(phenylmethyl)phenoxy]propyl]-1H-imidazole;

3a,4,5,6,7,7a-hexahydro-2-[[4-(phenylmethyl)phenoxy]propyl]-1H-benzimidazole;

2-[4-(phenylmethyl)phenoxy]-N-(tricyclo[3.3.1.1 3,7]decan-2-yl)ethanimidine, monohydrate;

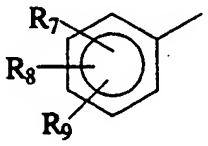
N'-hydroxy-2-[4-(phenylmethyl)phenoxy]ethanimidamide.

17. A pharmaceutical composition comprising a compound having the structure

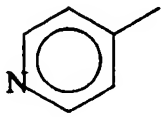
$$Ar_1\text{-}Q\text{-}Ar_2\text{-}O\text{-}(CH_2)_n\text{-}Z$$

and pharmaceutically acceptable salts and stereoisomers thereof, and a pharmaceutically acceptable carrier, wherein

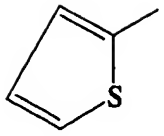
Ar^1 is an aryl moiety selected from the group consisting of:

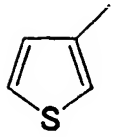
(i) 

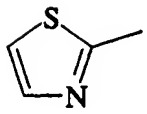
,

(ii) 

,

(iii) 

(iv)  , and

(v)  ;

Ar^2 is an aryl moiety selected from the group consisting of phenyl, mono-, di-, and tri-substituted phenyl, wherein the substituents are selected from the group consisting of Cl, Br, F, CF_3, lower alkyl, lower alkoxy, NH_2, NO_2, and OH;

Q is selected from the group consisting of:

(i) -O-;

(ii) $-CH_2-$,

(iii) $-OCH_2-$,

(iv) $-CH_2O-$,

(v) -NH-;

(vi) $-NHCH_2-$,

(vii) $-CH_2NH-$,

(viii) $-CF_2-$,

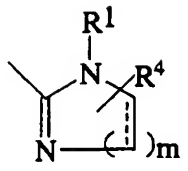
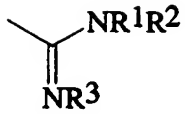
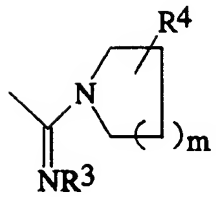
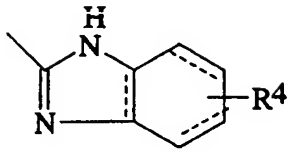
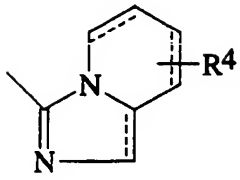
(ix) -CH=CH-,

(x) $-CH_2CH_2-$, and

(xi) carbon-carbon single bond;

n is 1, 2, or 3; and

Z is

wherein

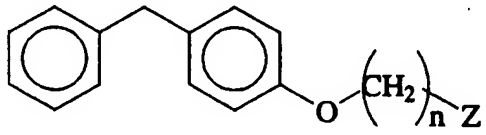
R^1, R^2 and R^3 are independently H, OH, lower alkyl, lower alkoxy, allyl, cyclic alkyl or $(CH_2)_p$-CO_2R^5 wherein p is an integer from 1 to 6;

R^4 is H, CO_2R^5, $CONH_2$, or COOH;

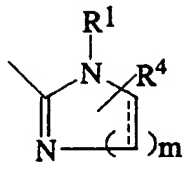
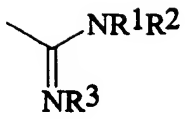
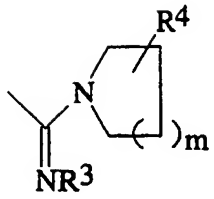
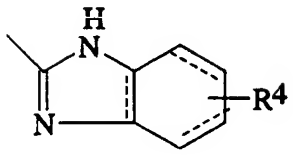
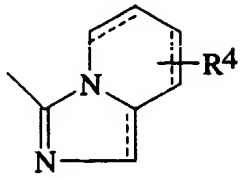
R^5 is H, lower alkyl, lower alkoxy, allyl or benzyl;

-------- represents a single or double bond; and m is 1 or 2.

18. The pharmaceutical composition of claim 17 wherein the compound has the structure:



wherein n is 1, 2, or 3 and Z is

wherein

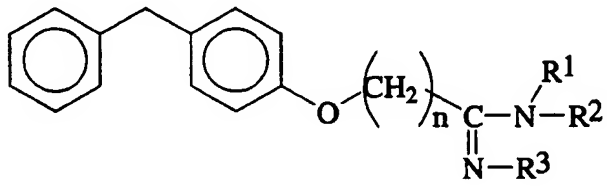
R^1, R^2 and R^3 are independently H, OH, lower alkyl, lower alkoxy, allyl, cyclic alkyl or $(CH_2)_p$-CO_2R^5 wherein p is an integer from 1 to 6;

R^4 is H, CO_2R^5, $CONH_2$, or COOH;

R^5 is H, lower alkyl, lower alkoxy, allyl or benzyl;

<u>--------</u> represents a single or double bond; and m is 1 or 2.

19. The pharmaceutical composition of claim 17 wherein the compound has the structure:



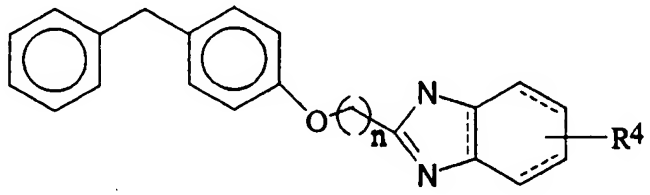
20. The pharmaceutical composition of claim 19 wherein in the compound R^2 is $(CH_2)_mCO_2R^5$.

21. The pharmaceutical composition of claim 20 wherein in the compound n is 1 and m is 2.

22. The pharmaceutical composition of claim 21 wherein in the compound R^1 and R^2 are independently hydrogen, lower alkyl, or cyclic alkyl.

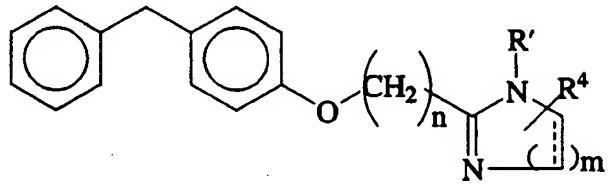
23. The pharmaceutical composition of claim 22 wherein in the compound R^3 is hydrogen or hydroxyl.

24. The pharmaceutical composition of claim 17 wherein the compound has the structure:



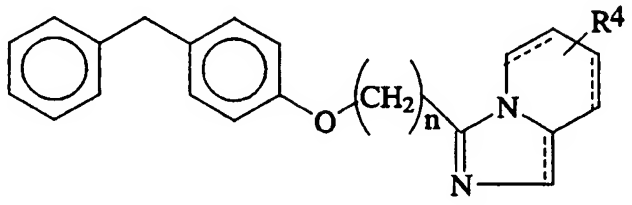
25. The pharmaceutical composition of claim 24 wherein in the compound R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

26. The pharmaceutical composition of claim 17 wherein the compound has the structure:



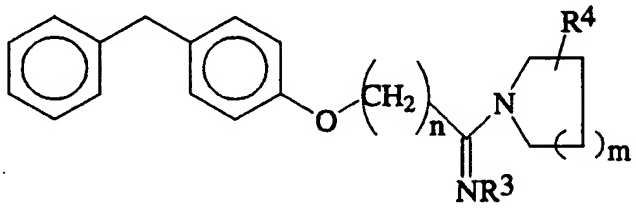
27. The pharmaceutical composition of claim 26 wherein in the compound R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

28. The pharmaceutical composition of claim 17 wherein the compound has the structure:



29. The pharmaceutical composition of claim 28 wherein in the compound R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

30. The pharmaceutical composition of claim 17 wherein the compound has the structure:



31. The pharmaceutical composition of claim 30 wherein in the compound R^3 is hydrogen or hydroxyl and R^4 is H, $CONH_2$, or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

32. The pharmaceutical composition of claim 17 wherein the compound is chosen from the group consisting of:

α-[[4-(phenylmethyl)phenoxy]methyl]-1-piperidinemethanimine, monohydrochloride;

α-[[4-(phenylmethyl)phenoxy]methyl]-1-pyrrolidinemethanimine, monohydrochloride;

ethyl 1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperdinecarboxylate, monohydrochloride;

ethyl 3-[[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]amino]propanoate, monohydrochloride;

4,5-dihydro-2-[[4-(phenylmethyl)phenoxy]methyl]-1H-imidazole;

1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl-4-piperidinecarboxyamide;

1-imino-2-[4-(phenylmethyl)phenoxy]ethanamine;

α-[3-[4-(phenylmethyl)phenoxy]propyl]-1-piperidinemethanimine, monohydrochloride;

4,5-dihydro-2-[3-[4-(phenylmethyl)phenoxy]propyl]-1H-imidazole;

3a,4,5,6,7,7a-hexahydro-2-[[4-(phenylmethyl)phenoxy]propyl]-1H-benzimidazole;

2-[4-(phenylmethyl)phenoxy]-N-(tricyclo[3.3.1.1 3,7]decan-2-yl)ethanimidine, monohydrate;

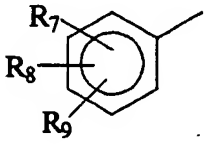
N'-hydroxy-2-[4-(phenylmethyl)phenoxy]ethanimidamide.

33. A method for treating an LTB_4-mediated inflammatory disease comprising administering to a mammal in need of treatment a therapeutically effective amount of a compound having the structure:

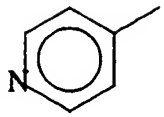
$$Ar_1\text{-}Q\text{-}Ar_2\text{-}O\text{-}(CH_2)_n\text{-}Z$$

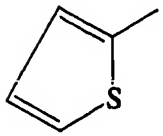
and pharmaceutically acceptable salts and stereoisomers thereof, and a pharmaceutically acceptable carrier, wherein

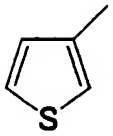
Ar^1 is an aryl moiety selected from the group consisting of:

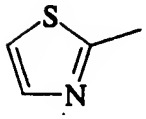
(i) 

,

(ii)  ,

(iii) 

(iv)  , and

(v)  ;

Ar^2 is an aryl moiety selected from the group consisting of phenyl, mono-, di-, and tri-substituted phenyl, wherein the substituents are selected from the group consisting of Cl, Br, F, CF_3, lower alkyl, lower alkoxy, NH_2, NO_2, and OH;

Q is selected from the group consisting of:

(i) -O-;

(ii) $-CH_2-$,

(iii) $-OCH_2-$,

(iv) $-CH_2O-$,

(v) -NH-;

(vi) $-NHCH_2-$,

(vii) $-CH_2NH-$,

(viii) $-CF_2-$,

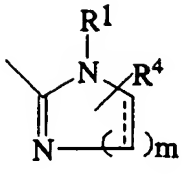
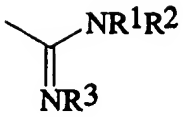
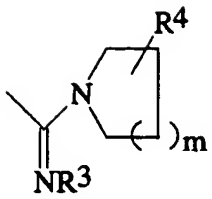
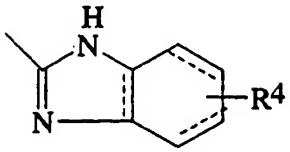
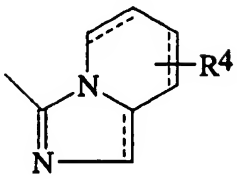
(ix) -CH=CH-,

(x) $-CH_2CH_2-$, and

(xi) carbon-carbon single bond;

n is 1, 2, or 3; and

Z is

wherein

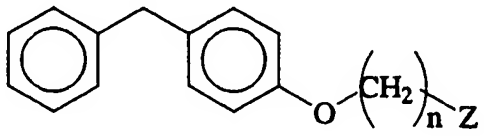
R^1, R^2 and R^3 are independently H, OH, lower alkyl, lower alkoxy, allyl, cyclic alkyl or $(CH_2)_p$-CO_2R^5 wherein p is an integer from 1 to 6;

R^4 is H, CO_2R^5, $CONH_2$, or COOH;

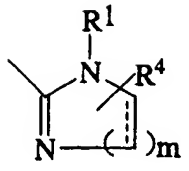
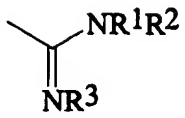
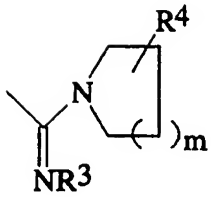
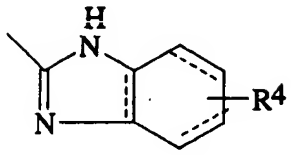
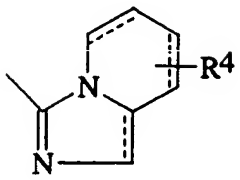
R^5 is H, lower alkyl, lower alkoxy, allyl or benzyl;

-------- represents a single or double bond; and m is 1 or 2.

34. The method of claim 33 wherein the compound has the structure:



wherein n is 1, 2, or 3 and Z is

wherein

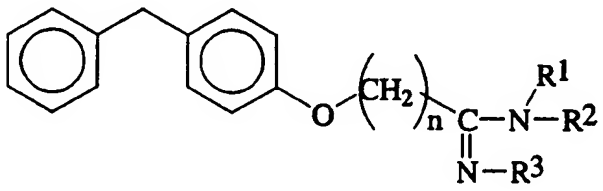
R^1, R^2 and R^3 are independently H, OH, lower alkyl, lower alkoxy, allyl, cyclic alkyl or $(CH_2)_p$-CO_2R^5 wherein p is an integer from 1 to 6;

R^4 is H, CO_2R^5, $CONH_2$, or COOH;

R^5 is H, lower alkyl, lower alkoxy, allyl or benzyl;

-------- represents a single or double bond; and m is 1 or 2.

35. The method of claim 34 wherein the compound has the structure:



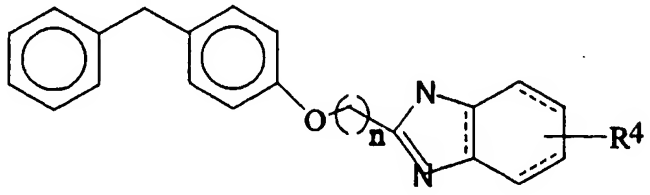
36. The method of claim 35 wherein in the compound R^2 is $(CH_2)_mCO_2R^5$.

37. The method of claim 36 wherein in the compound n is 1 and m is 2.

38. The method of claim 34 wherein in the compound R^1 and R^2 are independently hydrogen, lower alkyl, or cyclic alkyl.

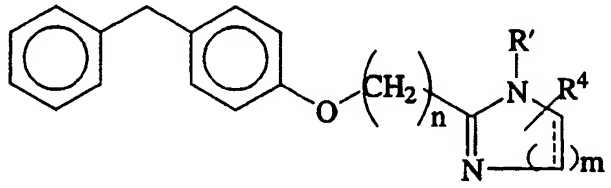
39. The method of claim 38 wherein in the compound R^3 is hydrogen or hydroxyl.

40. The method of claim 34 wherein the compound has the structure:



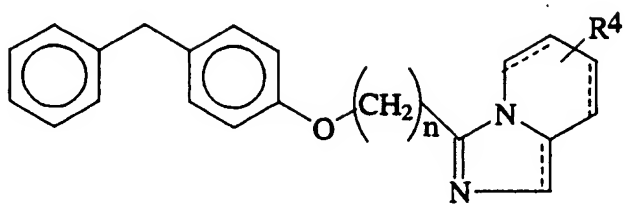
41. The method of claim 40 wherein in the compound R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

42. The method of claim 34 wherein the compound has the structure:



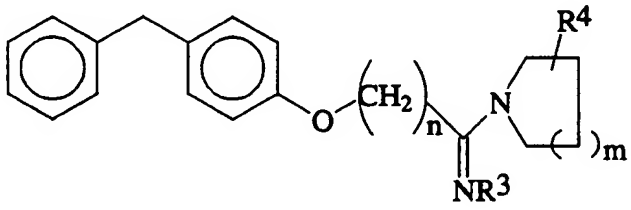
43. The method of claim 42 wherein in the compound R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

44. The method of claim 34 wherein the compound has the structure:



45. The method of claim 44 wherein in the compound R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

46. The method of claim 34 wherein the compound has the structure:



47. The method of claim 46 wherein in the compound R^3 is hydrogen or hydroxyl and R^4 is H or CO_2R^5 wherein R^5 is hydrogen, lower alkyl or benzyl.

48. The method of claim 34 wherein the compound is chosen from the group consisting of:

α-[[4-(phenylmethyl)phenoxy]methyl]-1-piperidinemethanimine, monohydrochloride;

α-[[4-(phenylmethyl)phenoxy]methyl]-1-pyrrolidinemethanimine, monohydrochloride;

ethyl 1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperdinecarboxylate, monohydrochloride;

ethyl 3-[[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl]amino]propanoate, monohydrochloride;

4,5-dihydro-2-[[4-(phenylmethyl)phenoxy]methyl]-1H-imidazole;

1-[1-imino-2-[4-(phenylmethyl)phenoxy]ethyl-4-piperidinecarboxyamide;

1-imino-2-[4-(phenylmethyl)phenoxy]ethanamine;

α-[3-[4-(phenylmethyl)phenoxy]propyl]-1-piperidinemethanimine, monohydrochloride;

4,5-dihydro-2-[3-[4-(phenylmethyl)phenoxy]propyl]-1H-imidazole;

3a,4,5,6,7,7a-hexahydro-2-[[4-(phenylmethyl)phenoxy]propyl]-1H-benzimidazole;

2-[4-(phenylmethyl)phenoxy]-N-(tricyclo[3.3.1.1 3,7]decan-2-yl)ethanimidine, monohydrate;

N'-hydroxy-2-[4-(phenylmethyl)phenoxy]ethanimidamide.

INTERNATIONAL SEARCH REPORT

In. itional Application No
PCT/US 98/03927

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/08 C07D211/62 C07D233/18 C07D235/12 C07D233/10
C07C257/14 A61K31/445 A61K31/155

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 11192 A (SEARLE & CO ;CHANDRAKUMAR NIZAL SAMUEL (US); CHEN BARBARA BAOSHENG) 18 April 1996 see the whole document ---	1-32
Y	WO 96 10999 A (SEARLE & CO ;CHANDRAKUMAR NIZAL SAMUEL (US); CHEN BARBARA BAOSHENG) 18 April 1996 see the whole document ---	1-32
Y	DE 41 21 849 A (RHONE POULENC RORER GMBH) 14 January 1993 see the whole document ---	1-32
A	WO 96 41625 A (SEARLE & CO) 27 December 1996 see the whole document ---	17
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

' Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 June 1998	09. 07. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In. ational Application No
PCT/US 98/03927

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document. with indication.where appropriate. of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 117, no. 11, 14 September 1992 Columbus, Ohio, US; abstract no. 111411, XP002068845 see abstract & R. LABAUDINIÈRE ET AL.: J. MED. CHEM., vol. 35, no. 17, 1992, pages 3156-3169, ---	1-32
A	CHEMICAL ABSTRACTS, vol. 126, no. 1, 1 January 1997 Columbus, Ohio, US; abstract no. 302, XP002068846 see abstract & J.H. YUAN ET AL.: DRUG METAB. DISPOS. , vol. 24, no. 10, 1996, pages 1124-1133, ---	1-32
X	CHEMICAL ABSTRACTS, vol. 53, no. 10, 25 May 1959 Columbus, Ohio, US; abstract no. 9194, XP002068847 see abstract & V.G. CAVALLINI ET AL.: FARMACO ED. SCI., vol. 11, 1956, PAVIA, pages 378-388, ---	1,2,10
X	EP 0 287 959 A (BASF AG) 26 October 1988 see page 77; example 30.1 -----	1,2,10

2

INTERNATIONAL SEARCH REPORT

mational application No.
PCT/US 98/ 03927

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 33-48
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 33-48 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition (Rule 39.1 iv) PCT)

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds which are encompassed by the general definition in the independent claims, the search had to be restricted for economic reasons. The search was limited to the prepared compounds for which pharmacological data are given (see Guidelines, Chapter III, paragraph 2.3). Additionally the rests R7, R8 and R9 are not defined and consequently no complete search could be made correspondingly.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
PCT/US 98/03927

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9611192 A	18-04-1996	US 5585492 A	17-12-1996
		AU 3686595 A	02-05-1996
		CA 2202371 A	18-04-1996
		EP 0804427 A	05-11-1997
		US 5719306 A	17-02-1998
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		EP 0843549 A	27-05-1998
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		CA 1331619 A	23-08-1994
		DE 3880544 A	03-06-1993
		ES 2054725 T	16-08-1994
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		KR 9610354 B	30-07-1996
		MX 9203407 A	01-08-1992
		SU 1655293 A	07-06-1991
		US 4943584 A	24-07-1990